REMARKS

Rejections of Claims and Traversal Thereof

In the July 14, 200e Office Action,

claims 1-8, 10, 11 and 73 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentabe over claims 1 and 3 of U. S. Patent No. 5,518,723 (DeVico, et al., hereinafter DeVico '723) in view of Chackerian, et al. (Proceedings of the National Academy of Sciences, March 1999);

claims 1-8, 10, 11, 24 and 73 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentabe over claims 1 of U. S. Patent No. 5,843,454 (DeVico, et al., hereinafter DeVico '454) in view of Chackerian, et al.; and

claims 1-3, 6-16 and 24 were rejected U.S.C. §103(a) as being unpatentable over Chackerian, et al. (Proceedings of the National Academy of Sciences, March 1999) and DeVico '454.

The rejection of claims 1-3, 6-16, 24 and 73 is hereby traversed, and reconsideration of the patentability of amended claims 1-3, 6-16 and 24 is requested, in light of the ensuing remarks.

Judicially Created Doctrine of Obviousness-type Double Patenting

1) Claims 1-8, 10, 11, and 73 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentabe over claims 1 and 3 of DeVico '723 in view of Chackerian, et al.

The initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention is always upon the examiner. *In re Oetiker*, 977 F.2d 1443,24 USPQ 1443, (Fed. Cir. 1992). The test for obviousness-type double patenting is whether the claimed invention of the subject application would have been obvious from the subject matter of the **claims** in the 'DeVico '723 in view of Chackerian, et al. *See In re Longi*, 774 F.2d 1100, 225 USPQ 645 (Fed.Cir. 1985). It

should be understood that the Office is not at liberty to resort to the text of the 'DeVico '723 specification for additional facts to support the obviousness-type double patenting. In all instances, only the literal statement of claims 1 and 3 of 'DeVico '723 may be considered in arriving at the conclusion of obviousness.

Applicants submit that claims 1 and 3 of 'DeVico '723 differ greatly from claims 1-8, 10-11 and 73 in the subject application by reciting *inter alia*, the addition of a spacer consisting of an amino acid sequence that links the virus coat polypeptide sequence and the receptor polypeptide sequence. Furthermore, the present invention provides for this spacer to be of a sufficient length to allow for an **intramolecular interacting complex** to form between the virus coat polypeptide sequence and the receptor polypeptide.

In contrast, the complex of DeVico '723 does not include a full length chain comprising an amino acid spacer positioned between the virus coat polypeptide sequence and the receptor polypeptide sequence, but instead the virus coat polypeptide sequence and the receptor polypeptide sequence are two separate entities that are **chemically cross-linked to form a permanent intermolecular covalent bond**. As stated in the second sentence of the "Detailed Description of the Embodiments" in the DeVico '723 patent at column 4,

> "We used a covalently linked gp120-CD4 complex as an immunogen. gp120 molecules were covalently coupled to soluble recombinant CD4 using bivalent cross-linking agents to ensure that the integrity of the complexes was maintained during any manipulations." (emphasis added)

Thus, the gp120 and the CD4 **were not a single chain** that folded properly to form an **intramolecular** complex but instead a covalent bond between the two separate entities was formed by a cross linking process. It should be noted that there is a vast difference between the meaning of the terms "intramolecular" and "intermolecular." The DeVico '723 patent discusses the special steps taken to ensure that this **covalent crosslinked intermolecular complex is made**, such as described in Example II, at column 6, lines 56-66;

> "The purified glycoprotein was coupled to sCD4 (commercially obtained from Dupont) by using bis (sulfosuccinimidyl) suberate (BS) (Pierce) as a crosslinker. For this gp120 and sCD4 were mixed at 1:2 molar ratio in PBS and incubated at 37

°C for 1 hr followed by treatment with 0.5 mM BS at room temperature for 1 hr. The complex was further incubated overnight at 4°C. The excess BS was blocked with 20 mM Tris-HCl (pH 8.0)."

Applicants contend that it is patentably distinct to provide full length polypeptide sequence that includes a spacer consisting of an amino acid sequence that binds to the virus coat polypeptide sequence and the receptor polypeptide and positioned therebetween especially when **neither the claims nor full text** of the 'DeVico '723 reference **teach or suggest such an amino acid sequence spacer**. Furthermore, applicants claimed invention recites "an **intramolecular interacting** complex, wherein the intramolecular interacting complex exhibits reactivity relative to an uncrosslinked complex comprising a soluble virus coat polypeptide sequence and a viral receptor polypeptide sequence."

The Office has cited Chackerian et al. as prior art for showing that this amino acid sequence spacer positioned between the virus coat polypeptide sequence and the receptor polypeptide amounts, which are a ligand/receptor pair, is an obvious modification of the invention recited in claims 1-8, 10, 11, and 73. Chackerian, et al. relates to a method for disguising self-proteins for recognition as foreign antigens. Chackerian, et al. describes inserting a native self-protein, which was an extracellular (EC) loop of the mouse C-C chemokine receptor CCR5, into the viral capsid (L1) protein from bovine papillomavirus type 1. The chimeras of Chackerian, et al. were constructed by inserting the mCCR5 within the sequence for L1, that being the mCCR5 protein was **flanked on both sides by sequences of the L1 protein**. Specifically, as stated at page 2372 in column 2, the mCCR5 replaced amino acids 130-136, 275-285, or 344-350 of the L1 sequence.

Initially, it should be noted that there is no teaching or suggestion that the self-protein and the viral capsid protein of Chackerian, et al. have any affinity for binding to each other when they are combined into the chimeric polypeptide. Thus, they are certainly not a **receptor/ligand pair**. Further, there is no teaching or suggestion to separate the two proteins by an amino acid spacer that is of a sufficient length of amino acid residues to allow the polypeptide to fold and form an **intermolecular interacting complex** between the two different proteins that are a receptor-ligand pair. Instead, the bovine papillomavirus has the intrinsic capacity to self-assemble into virus like particles that induce high levels of neutralizing antibodies.

Clearly, the combination of DeVico '723 and Chackerian, et al. do not teach or suggest the formation of an **intramolecular interacting complex** between the viral coat polypeptide sequence and the viral receptor polypeptide sequence wherein the **intramolecular complex** exhibits reactivity relative to a uncrosslinked complex comprising a soluble virus coat polypeptide sequence and a viral receptor polypeptide sequence. Applicants question how the covalently bonded complex of DeVico '723 falls within the present claims when the presently claimed invention does not include a crosslinked covalent bond but instead an intramolecular complex that exhibits the reactivity of an uncrosslinked complex? Moreover, applicants' claimed invention does not fall within the claims of DeVico '723.

Because the Office has not provided the applicants with any factual basis and/or rationale to support the conclusion that the claimed invention is an obvious variation of DeVico '723 in view of Chackerian, et al. the double patenting rejection of claims 1-8, 10-11 and 73 cannot stand. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

2) Claims 1-8, 10, 11, 24 and 73 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentabe over claim 1 DeVico '454, in view of Chackerian, et al. Applicants traverse this rejection and state that the proposed combination suffers from the same shortcomings as the previously proposed combination.

Specifically DeVico '454 state at column 4, lines 47-51, that:

> "We used a covalently linked gp120-CD4 complex as an immunogen. gp120 molecules were covalently coupled to soluble recombinant CD4 using bivalent cross-linking agents to ensure that the integrity of the complexes was maintained during any manipulations." (emphasis added)

Furthermore, all the examples discussed in this issued patent discuss the steps required to bind the separate entities gp120 and CD4 by means of a crosslinking agent. For example, at column 7, lines 2-5, it is stated that:

"The purified gp120 was then crosslinked to sCD4 (DuPont) using the noncleavable, water-soluble crosslinker, bis(sulfosuccinimidyl) suberate (BS)."

In Example II, at column 8, lines 1-7, the preparation of the crosslinked covalent complex was described:

"The purified glycoprotein was coupled to sCD4 (commercially obtained from DuPont) by using bis (sulfosuccinimidyl) suberate (BS) (Pierce) as a crosslinker. For this gp120 and sCD4 were mixed at 1:2 molar ratio in PBS and incubated at 37°C for 1 hr followed by treatment with 0.5 mM BS at room temperature for 1 hr. The complex was further incubated overnight at 4 °C. The excess BS was blocked with 20 mM Tris-HCl (pH 8.0)."

The reasoning for the importance of such crosslinking to form the covalent bond is discussed at column 4, lines 66 to column 5, line 2, wherein the DeVico '454 patent states that:

"Given the transient and short-lived nature of the native gp120-CD4 complex, it is unlikely that it is presented to the immune system in such a way as to elicit complex-specific antibodies."

Thus, again any complexes described in DeVico '454 and Chackerian, et al. do not teach or suggest the formation of an **intramolecular interacting complex** between the viral coat polypeptide sequence and the viral receptor polypeptide sequence wherein the **intramolecular complex** exhibits reactivity relative to a uncrosslinked complex.

In contrast, applicants discussed at page 45 of the present application and found that the FLSC chimeric polypeptides of the present claimed invention showed reactivity relative to the non-covalent and uncrosslinked complex gpl20-rsCD4.

Figure 5A shows that all of the antibodies reacted strongly with the FLSC. However, the half-maximal binding concentrations of antibodies 17b, 48d, and A32 were consistently higher with FLSC and equivalent to what was observed with soluble, non-covalent BaLgp120-rsCD4 complexes. Thus, these results demonstrate that gp120-CD4 chimeric polypeptide reactivity was comparable to that observed with complexes made by combining soluble gp120 and CD4 (uncrosslinked), and higher than with gp120 alone. These data indicate that the single-chain

gp120-CD4 molecules of the present invention formed interacting complexes similar to the transition state HIV envelope-CD4 complex, which is considered to be an affinity interaction. Thermodynamic studies indicate that free gp120 is a disordered molecule that continually "samples" conformations in solution. CD4 binding "induces" a more ordered gp120 conformation. Direct interatomic contacts between CD4 and gp120 involve some CD4 residues and gp120 residues. These interatomic contacts include Van der Waals contacts and hydrogen bonds. Thus, the interacting complex formed between the gp120 and CD4 peptides linked by a foldable amino acid spacer is due to natural affinity.

Again, because the Office has not provided the applicants with any factual basis and/or rationale to support the conclusion that the claimed invention is an obvious variation of DeVico '454 in view of Chackerian, et al. the double patenting rejection of claims 1-8, 10-11, 24 and 73 cannot stand. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 1-3, 6-16 and 24 were rejected U.S.C. §103(a) as being unpatentable over Chackerian, et al. and DeVico '454. Applicants submit that the combination of the two cited references does not in any way render applicants' claimed invention *prima facie* obvious.

The present invention relates to a single chain chimeric polypeptide that includes a virus coat polypeptide sequence, a viral receptor polypeptide sequence that has a bonding affinity for the virus coat polypeptide sequence, and an amino acid sequence spacer having a first end linked to the virus coat polypeptide sequence and the opposite end linked to the viral receptor polypeptide sequence to form a single chain polypeptide, wherein the amino acid spacer consists of a sufficient length of amino acid residues to allow the single chain chimeric polypeptide to fold thereby permitting the virus coat polypeptide sequence and the viral receptor polypeptide sequence to form **an intramolecular interacting complex**. Importantly, this intramolecular interacting complex exhibits reactivity relative to a uncrosslinked and non-covalent complex comprising a soluble virus coat polypeptide sequence and a viral receptor polypeptide sequence.

In contrast, claim 1 of DeVico '454 recites:

> "A composition comprising: an immunogenic complex comprising **gp120 covalently bonded** to CD4; and an adjuvant composed of aluminum phosphate gel." (emphasis added)

According to the Office, the claims or specification of DeVico '454 does not limited the complexes to the use of a chemical crosslinker. Applicants vigorously disagree because as stated above, each and every example set forth in the DeVico '454 specification describes the use of the a chemical crosslinker to form the covalent bond.

DeVico et al. expressly stated at column 2, lines 42-45, that "immunization with soluble CD4 and recombinant gp120, complexed by their natural affinity but not covalently bonded, resulted in the production of anti CD4 antibodies (31)," and as such, DeVico '454 recognized that the natural bonding between CD4 and gp120 through natural affinity included Van der Waals attractions and hydrogen bonding. However, to overcome the perceived problems with natural affinity bonding, they chose to chemically bind the gp120 to the CD4.

In sharp contrast, the complexes of DeVico '454 are **chemically coupled** as stated numerous times in the specification.

For example, at the bottom of column 1, it is stated that

> "We have overcome the shortcomings of type specific anti gp120 antibodies and antibodies against CD4 by raising anti-HIV-1 neutralizing antibodies using as the immunogen a complex of gp120 **chemically coupled** to either soluble CD4 or to the mannose-specific lectin, succinyl concanavalin A (SC). We have found that these compounds induce similar conformational changes in gp120. The complexed gp120 appears to undergo a conformational change that presents an array of epitopes that were hidden on the uncomplexed glycoprotein (2)." (emphasis added)

Moreover, in the "Summary of Invention" (column 3), it is stated that:

> "We used **chemically-coupled** gp120-CD4 complexes as immunogens for raising neutralizing antibodies. We found that gp120-CD4 complexes possess novel epitopes that elicit neutralizing antibodies." (emphasis added)

Still further, as stated at the bottom of column 6, the complexes were chemically coupled;

> "c. Immunological properties of chemically coupled gp120-CD4 complexes:
>
> We demonstrated that gp120-sCD4 complexes are immunogenic and capable of eliciting HIV-1-neutralizing antibodies. An immunoaffinity procedure was used to purify gp120 from chronically-infected H9/HIV-1.sub.IIIB cells. The purified gp120 was then **crosslinked** to sCD4 (DuPont) using the noncleavable, water-soluble crosslinker, bis(sulfosuccinimidyl) suberate (BS)." (emphasis added)

As such, the specification and the claims of DeVico '454 clearly state that the covalent bond is chemically formed. The Office's speculation that a crosslinking agent does not form the covalent bond is completely without support in the DeVico '454 specification. There are only two types of bonds discussed in DeVico '454, one limited to the natural affinity bond between gp120 and CD4 that the reference goes on to state that this affinity bond is unstable, and then a discussion of the chemically formed covalent bond formed by the use of a crosslinking agent to overcome the unstableness of the natural affinity bond.

The Office further states, that "Chackerian, et al. discloses producing an auto-antibody to the 'cryptic' epitope structures of CCR5 which are exposed by the chimera." Applicants are at an absolute loss to find such a disclosure in Chackerian, et al. The CCR5 sequence was inserted into the viral capsid to determine if the immune system could be tricked and antibodies would be generated for a self-protein. There is no disclosure regarding an epitope that is only visible after the binding of one sequence to another. There is no doubt that the CCR5 epitope was always visible, but the body would not generate antibodies against the self-protein, thus the reasoning for inserting it among a viral antigen.

The Office further states: "That conformation is an important aspect in these chimera is indicated by the fact that denatured L1-CCR5 chimeras did not induce antibody formation to CCR5, only in the context of the folder complex is there antibody production against the receptor." Firstly, it should be recognized that if CCR5 is the cryptic epitope then it should only be visible after the viral capsid is formed. However, this is not true, the CCR5 is inserted and merely becomes a

very small part of the viral capsid. There is no discussion that the tertially structure formed by the viral capsid exposed a novel unknown epitope of CCR5.

According to the Office:

> "it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex. . . . One having ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to achieve the conformation complex as taught by DeVico, et al. which would have the advantage of requiring less process steps in order to achieve the same function."

Applicants vigorously disagree. Clearly the DeVico '454 reference gives no indication that a shortcut would improve the described covalently bonded complex. DeVico '454 requires crosslinking because as stated numerous times in the reference, covalent bonding of the gp120 protein to the CD4 by crosslinking is very important to maintain the integrity of the complex. There is no suggestion to produce a complex that is not covalently bonded because of the cited problems with complexes that were not covalently bonded. Applicants suggest that if the DeVico '454 crosslinked complexes were made according to the methods described by Chackerian, et al. then the DeVico '454 complexes would no longer be chemically crosslinked and thus would not function as intended. According to the court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

Moreover, what is the asserted motivation put forth in either reference to insert amino acid sequence between the different peptides of either reference for the purpose to enhance folding and/or complex forming? After a thorough review of DeVico '454, applicants cannot find any motivation to form a single chain polypeptide that includes the virus coat polypeptide sequence and the viral receptor polypeptide separated by an amino acid spacer. Instead, DeVico '454 stresses the importance of chemically coupling the gp120 protein directly to the CD4 receptor protein to ensure that the two soluble proteins are not separated when in use.

DeVico '454 discusses numerous times the instability of the prior art complexes, and the fact that unless the two proteins were crosslinked the two proteins would separate and antibodies would not be produced for the cryptic epitope but instead one of the uncomplexed proteins. For example, as discussed at column 2, lines 42-45 "Immunization with soluble CD4 and recombinant gp120, complexed by their natural affinity but not covalently bonded, resulted in the production of anti CD4 antibodies." It is further stated in column 2, that "the complexes used in these studies were unstable and comprised noncovalently bound gp120 and CD4." To overcome the shortcomings of the discussed prior art, DeVico '454, as stated at column 4, lines 46-51, "used a covalently linked gp120-CD4 complex as an immunogen. gp120 was covalently coupled to soluble recombinant CD4 using bivalent cross-linking agents to ensure that the integrity of the complexes was maintained during any manipulations."

Considering the importance of the covalent bond between the gp120 and CD4 proteins and the discussion that a noncovalently bonded complex was not effective, applicants submit that DeVico '454 teaches away from applicants' claimed single chain polypeptides. Clearly, one reading DeVico '454 would not be provided with any incentive to insert an amino acid spacer between the virus coat protein and the viral receptor protein. Nor is there any indication that such a complex would be effective, especially because applicants' formed complex is maintained by natural affinity. DeVico '454 teaches that forming a noncovalently bonded complex has several inherent problems such as the two soluble proteins becoming uncomplexed and this was the impetus for DeVico '454 to form a covalent bond between the gp120 and the CD4 by crosslinking the two soluble proteins together.

However, applicants have shown that if the amino acid sequence spacer is of sufficient length, a stable complex can form and this fact is proven in the results of the examples set forth in the present application. Specifically, in Example 3, the single chain polypeptides of the present invention were tested using monoclonal antibodies that previously have been shown to preferably bind gp120 only after engagement with CD4. The binding of these monoclonal antibodies with the single chain gp120-CD4 molecules of the present invention showed that a properly folded gp120-CD4 was formed.

The Office has not identified any objective or specific teachings or suggestions in the cited references that would motivate one skilled in the art to combine the references. Neither reference uses an amino acid spacer, Chackerian, et al. does not teach or suggest a receptor/ligand pair but instead inserting self proteins in a viral capsid protein in an acceptable order to trick the body into believing that the self protein is in fact a foreign antigen and DeVico '454 teaches the importance of **chemically crosslinking two soluble** proteins into a covalently bonded complex.

Surely one skilled in the art would never consider combining the two references and uncrosslink the DeVico '454 complex and put the two soluble proteins into the Chackerian, et al. arrangement and then somehow determine that an amino acid sequence of a sufficient length positioned between the two proteins would allow for a stable complex, absent a reading of applicants' present application. Thus, the Office seems to be merely reinterpreting the prior art in light of applicants' disclosure, in order to reconstruct applicants' claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

In light of the above discussion and the fact that the Office has not met its burden of establishing a *prima facie* case of obviousness, applicant requests that the rejection of claims 1-3, 6-11, 13-16 and 24, on the basis of obviousness, be withdrawn.

Drawings

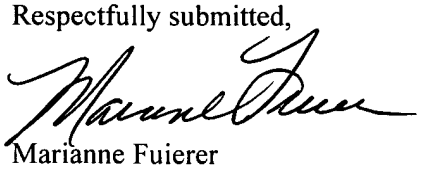
Applicants include herewith a new set of formal drawings that meet all requirements of 37 CFR §1.84.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Winkler reconsider the patentability of claims 1-3, 6-11, 13-16, 24 and 73 in light of

the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Winkler is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



Marianne Fuierer
Attorney for the Applicants
Registration No. 39,983

INTELLECTUAL PROPERTY/
Technology Law
P.O. Box 14329
Research Triangle Park, NC 27709
Telephone: (919) 419-9350
Facsimile: (919) 419-9354
IPTL File: 4115-144